II. REMARKS

A. Status of Claims

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are pending in this application. The claims of the present application have not been amended in this response.

B. 35 U.S.C. §112, First Paragraph Rejection of Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71, and 76-81 for Lack of Written Description

In the Advisory Action, the Examiner did not make specific reference to this 35 U.S.C. §112, first paragraph rejection, but did state that "[t]he claims remain rejected [as] set forth in the Final Office Action of 7/12/05". In the Final Office Action, the Examiner stated the following:

> In the amendment of 5/9/05 applicant deleted the phrase "about"; however a careful review of the specification does not provide support for this. For instance, the instant specification provides a Tmax of **about** 10 to 32 hours wherein the specific range of 10 to 32 hours is not contemplated. The limitation removing "about" in claim 76, 77, and 80 also is not supported. If applicant contends there is support for such an amendment, the examiner requests the applicant point to the specific page and line where support may be found.
>
> Final Office Action dated July 21, 2005 at page 2 (*emphasis in original*).

This rejection is traversed. It is respectfully submitted that the disclosure of a range including a lower limit of "about 10" does provide literal support for a claimed lower limit of "10" and that one skilled in the art would consider the claimed range literally supported by the original disclosure. The use of the term "about" expands the scope of the term it is describing and "the use of the word 'about' avoids a strict numerical boundary to the specified parameter." *Pall Corp. v. Micron Separations, Inc.*, 36 USPQ2D (BNA) 1225, 1229 (Fed. Cir. 1995). This position supports the conclusion that the specified parameter which is modified by the term "about" is literally supported by such a disclosure.

Therefore, it is respectfully submitted that one skilled in the art would consider the term "about 10" as literally supporting the value of "10" itself.

Further, the CCPA in *In re Wertheim*, 191 USPQ 90 (CCPA 1976) stated that the Patent and Trademark Office has the initial burden of presenting evidence or reasons why persons skilled in art would not recognize in the disclosure, a description of the invention defined by the claims; pointing to the fact that claims reading on embodiments outside the specification's scope satisfies this burden. See *In re Wertheim*, 191 USPQ at 97. In the present application, the Examiner has not met this burden as the claimed range of "10 to about 32 hours" does not read on embodiments outside the specification's scope of "about 10 to about 32 hours".

The CCPA in *In re Wertheim* further stated that with the applicants specification describing a range of 25% - 60% and specific examples of 36% and 50% supported the claimed range of 35% to 60%. See *id.* at 98. The CCPA stated that "the PTO has done nothing more than to argue lack of literal support which is not enough," and "[i]f lack of literal support alone were enough to support a rejection under §112, then the statement of *In re Lukach* [169 USPQ 795], that 'the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of § 112 ,' is empty verbiage." *Id.* at 98. (emphasis added). The CCPA further stated that "[t]he burden of showing that the claimed invention is not described in the specification rests on the PTO in first instance, and it is up to the PTO to give reasons why description not in *ipsis verbis* is insufficient." *Id.* (emphasis added).

In the present application, it is respectfully submitted that the Examiner has taken the position that "10" is not supported literally (i.e., *ipsis verbis*) by "about 10" and has not presented any evidence to meet the burden of proof for this position, other than by stating that the disclosure lacks support for the claimed range. However, it is respectfully submitted that persons skilled in art would recognize the disclosure of "about 10" as supporting the value of "10" itself.

Accordingly, it is respectfully submitted that claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71, and 76-81 do not lack written description under 35 U.S.C. §112, first paragraph and respectfully request that this rejection be withdrawn.

C. 35 U.S.C. §102 Rejection of Claims 1-13, 18-19, 21-22, 25-54, 57-71, and 76-81 Based Upon U.S. Patent No. 5,376,383 to Alberts et al.

In the Final Office Action, claims 1-13, 18-19, 21-22, 25-54, 57-71, and 76-81 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,376,383 to Alberts et al. (hereinafter "the Alberts reference). In the Final Office Action, the Examiner stated the following:

> Alberts discloses a method of lowering plasma cholesterol levels by administering to a subject a time-controlled drug-delivery device containing a water-soluble HMG-CoA reductase inhibitor (lovastatin, pravastatin, etc.). Alberts discloses that using a sustained or controlled release provides for a single dose to yield an equivalent or improved effect as that of a rapid release formulation (col. 1, lines 39-50 and abstract). . . . The examples provide a controlled device comprising a core and a coat, which is substantially similar to instant disclosure Table 1's general formula.
>
> Note that although the prior art does explicitly state the instant functional limitations, it is the examiner's position that the instant functional limitation is inherent since Albert's example 10 provides a release rate over an 18 hour period. Thus, the Tmax would inherently fall within [the] instant range. The recitation of a newly discovered function inherently possessed by the prior art, does not make distinguish it from the prior art. Further it is applicant's burden to prove otherwise.

Final Office Action of July 21, 2005 at pages 3-4 (*citations omitted*).

In the Advisory Action, the Examiner responded to Applicants arguments in the response to Final Office Action, as follows:

> With regard to the 102 rejection over Alberts, the examiner points out that, the examiner has made a reasonable rationale for inherency and it is the applicants burden to prove it is not inherent with evidence. Note MPEP 716.01 II wherein it clearly states that the attorney arguments cannot [take] the place of evidence.

Advisory Action of December 22, 2005 at page 2.

This rejection is traversed. It is respectfully submitted that the Alberts reference fails to teach the claimed Tmax parameters, and the claimed dissolution profiles as recited in the present claims.

Specifically, the Alberts reference fails to teach a controlled release dosage form or a method of treatment with a controlled release dosage form, which provides the following:

a. a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration as recited in claims 1, 48, 70, and 71;

b. a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration as recited in claim 51;

c. a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration as recited in claim 58;

d. a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours as recited in claim 62;

e. a dissolution rate as recited in claim 71;

f. a mean time to maximum plasma concentration (T_{max}) of lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime as recited in claims 76 and 78;

g. a mean time to maximum plasma concentration (T_{max}) of lovastatin which occurs at 10.6 to 23.2 (16.9 ± 4.5) hours after oral administration to human patients at bedtime as recited in claims 77 and 79; or

h. a mean time to maximum plasma concentration (Tmax) of lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal as recited in claims 80 and 81.

Example 10, which is cited by the Examiner, merely states that the formulation gave an 85% release over 18 hours and does not provide any indication or suggestion for correlating a mean time to maximum plasma concentration (T_{max}).

Further, submitted herewith as Exhibit A is Gregory A. McClelland, et al., Enhancement of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form, Pharmaceutical Research, Vol. 8., No. 7. 1991. At page 874, McClelland, et al. describes a formulation which is substantially similar to the formulation described in Example 3 of Alberts. The formulation of McClelland, et al. provides approximately 90% release after 24 hours as indicated on page 875. McClelland, et al. indicates *in vivo* data with respect to this formulation, and in particular, the Examiner's attention is directed to Figure 2 on page 875 of McClelland, et al. It is respectfully submitted that to the extent that dog data is instructive with respect to humans, Figure 2 would indicate to one of ordinary skill in the art that the formulation of McClelland, et al. (which is substantially similar to the formulation of Example 3 of Alberts) would not provide a T_{max} of 10 to about 32 hrs, as recited in the claims of the present application.

Contrary to the Examiner's allegations, the examples in Alberts are not substantially similar to the general formula presented in Table I of the instant application, and therefore, the Examiner has not made a reasonable rationale for inherency and has not shifted the burden to the Applicants to prove it is not inherent with evidence.

Although the claims are not limited by the general formula in Table I, the table shows that a tablet that can be modified to exhibit the claimed pharmacokinetic parameters can contain a) an inner core containing an alkyl ester of a substituted naphthalene, a water swellable polymer, and an osmotic agent and b) an outer coating containing an enteric polymer and a water-insoluble polymer. In contrast, Alberts describes tablets with cores that **do not** contain water swellable polymers (examples 3-7) and tablets that contain drug mixed with a water swellable polymer, but **do not** have an outer coating containing an enteric polymer and a water-insoluble polymer (examples 8-16). Moreover, the exemplified formulations which exhibit the pharmacokinetic data, of the instant claims contain a core, a seal coat, an inner coating containing an enteric polymer, an outer coating containing an enteric polymer and a water insoluble polymer, and an optional overcoat (see examples 5-9 on pages 35-38; pages 40-44; and tables 6-8).

Since the formulations described by Alberts are remarkably different from those taught by the present application, one can not say that the reference inherently discloses the pharmacokinetic parameters and dissolution profiles of the claimed controlled release dosage forms. It is noted that the present claims are not limited to the exemplified formulations and that other formulations which exhibit the claimed pharmacokinetic parameters are encompassed by the claimed invention. For example, pages 19 to 24 of the present specification disclose many different types of formulations which can be modified to provide the claimed pharmacokinetic parameters.

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). See also, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

It is respectfully submitted that the Examiner has not met her burden of proof to make an inherency rejection as there is no indication in the Alberts reference that the claimed Tmax of the present invention must be "necessarily present" in the formulations described in the reference.

The Examiner's basis for inherency appears to be based on Alberts' Example 10 providing a release rate over an 18 hour period. In view of McClelland et al. above, which describes a substantially similar formulation to the formulation described in Example 3 of Alberts, and which provides approximately 90% release after 24 hours, the Examiner's basis that a formulation providing a certain release rate would inherently provide a T_{max} falling within the range of the present claims is incorrect.

It is further submitted that if one skilled in the art were able to manipulate the formulations of Alberts to achieve a formulation which met the present claimed limitations, one would have to optimize conditions, ingredients and parameters. For example, critical parameters such as compression force, particle size of initial ingredients, and temperature/humidity conditions are not specified in the Alberts reference.

Further, due to the lack of such critical parameters (e.g., compression force, particle size of initial ingredients, and temperature/humidity conditions) in the Alberts reference, Applicants are unable to compare the instant invention's T_{max} and that of the prior art, as suggested by the Examiner. Also, it is respectfully submitted that that it would be unethical for the Applicants to conduct human clinical trials for the sole purposes of establishing patentability.

As the Alberts reference does not expressly or inherently teach the presently claimed invention, the Examiner is respectfully requested to withdrawal this rejection.

D. 35 U.S.C. §103 Rejection of Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 Based Upon U.S. Patent No. 5,837,379 to Chen et al.

In the Final Office Action, the Examiner rejected claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 under 35 U.S.C. §103(a) as being obvious over the Chen et al.

In the Final Office Action, the Examiner stated the following:

> Chen et al disclose a once daily pharmaceutical tablet having a 1) compressed core contains a medicament, a water-soluble osmotic compound, and one or more osmotic polymers, and 2) a membrane coating containing a water insoluble pharmaceutically acceptable polymer and an enteric polymer. See abstract. Although nifedipine is exemplified, Chen teaches various water-insoluble medicaments that may be utilized, including instant lovastatin. See column 2, line 64.
>
> . . . .
>
> It is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Chen et al and include the instant lovastatin in the controlled release dosage form. One would have been motivated to do so since Chen teaches a variety of medicaments that would benefit from the use of the instant controlled release formulation and teaches the

> instant active as one of the suitable medicaments. Therefore, one could reasonably expect similar results by including lovastatin in Chen's controlled release device.
>
> Furthermore, it is the examiner position that the instant controlled release device would meet the instant functional limitations since Chen's controlled release device is similar in structure and formulation to applicant's dosage form described in the specification; in particular Table 1. Therefore, it is the examiner's position that both would function similarly if not the same since the structures of the instant invention and that of the prior art are the same.

Final Office Action of July 21, 2005 at pages 7-8.

In the Advisory Action, the Examiner responded to Applicants arguments in the response to Final Office Action as follows:

> With regard to the obviousness rejection over Chen, the examiner has not argued that nifedipine and lovastatin have similar structures, rather the examiner has argued that the controlled release dosage form taught by Chen is structurally similar to applicant's. Thus it is the examiner's position that the controlled release dosage form would provide the instantly claimed Tmax. The examiner notes that lovastatin is not exemplified and is taught as a suitable drug among other drugs, thus the examiner has made the rejection under obviousness wherein the criteria for obviousness is that the prior art provides some suggestion or motivation to utilize the instantly claimed drug. In instant case, Chen teaches lovastatin is a suitable drug to utilize in the dosage form.

Advisory Action of Dec. 22, 2005 at page 2.

This rejection is traversed. Chen et al. is directed to controlled release dosage forms and only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 51 to column 3, line 11 of Chen et al.) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.). The only data provided in this patent directed to in-vivo results is data directed to dosage

forms of nifidepine, which is not in any way related to, e.g., an alkyl ester of hydroxy substituted naphthalenes. None of the exemplified formulations includes a drug that is an alkyl ester of hydroxy substituted naphthalenes, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone an alkyl ester of hydroxy substituted naphthalenes. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that the *in vivo* plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the alkyl esters of hydroxy substituted napthalenes. Therefore, there is no motivation in Chen to produce dosage forms of these compounds having the claimed pharmacokinetic parameters. The present application clearly demonstrates the benefits and need for these dosage forms in Table 12, which shows the advantage of a formulation of the present invention (Lovastatin XL) over immediate release Mevacor®, with respect to changes in LDL- cholesterol, HDL-cholesterol, Total Cholesterol, and Triglycerides.

It is respectfully submitted that one skilled in the art would not be motivated to select the particular claimed agent (i.e., an alkyl ester of hydroxy substituted naphthalenes) from the large genus disclosed at column 2, line 51 to column 3, line 11 of Chen et al. In support of this position, it is respectfully submitted that with respect to Chen et al., (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed agent; and (iii) there is no teaching of structural similarity in the reference. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(A-C). A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382,

29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the claimed species or subgenus must be taught by the prior art. See e.g., *In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215.

It is respectfully submitted that the size of the possible active agents which can be used in accordance with Chen et al. is sufficiently large as not to inherently disclose each and every individual species (in this case, lovastatin, fluvastatin, simvastatin, and pravastatin) which falls within their broad genus.

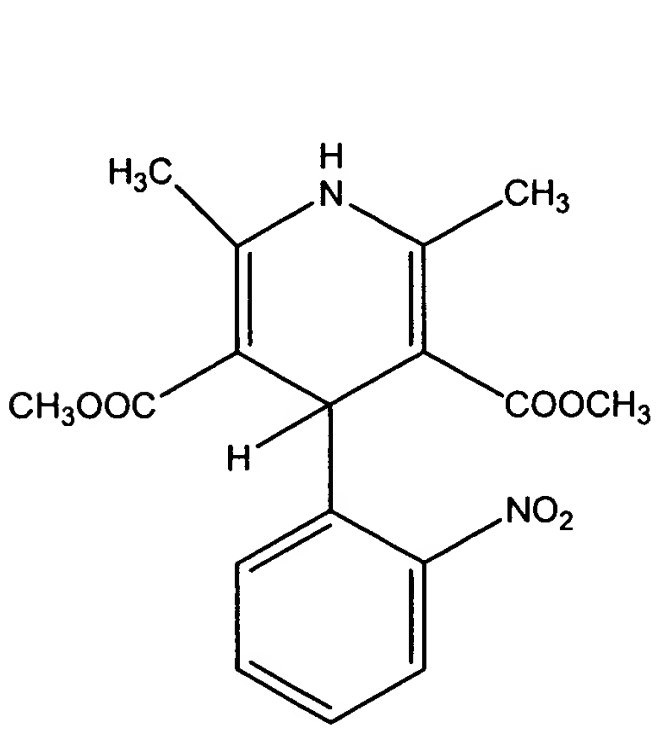
(ii) The reference does not expressly teach a particular reason to select the claimed agent

If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of lovastatin, fluvastatin, simvastatin, and pravastatin in Chen et al. is embedded within a large genus. Accordingly, the Chen et al. reference does not expressly teach a particular reason to select an alkyl ester of hydroxy substituted naphthalenes, such as lovastatin, from the plethora of other possible species in the genus of the reference.

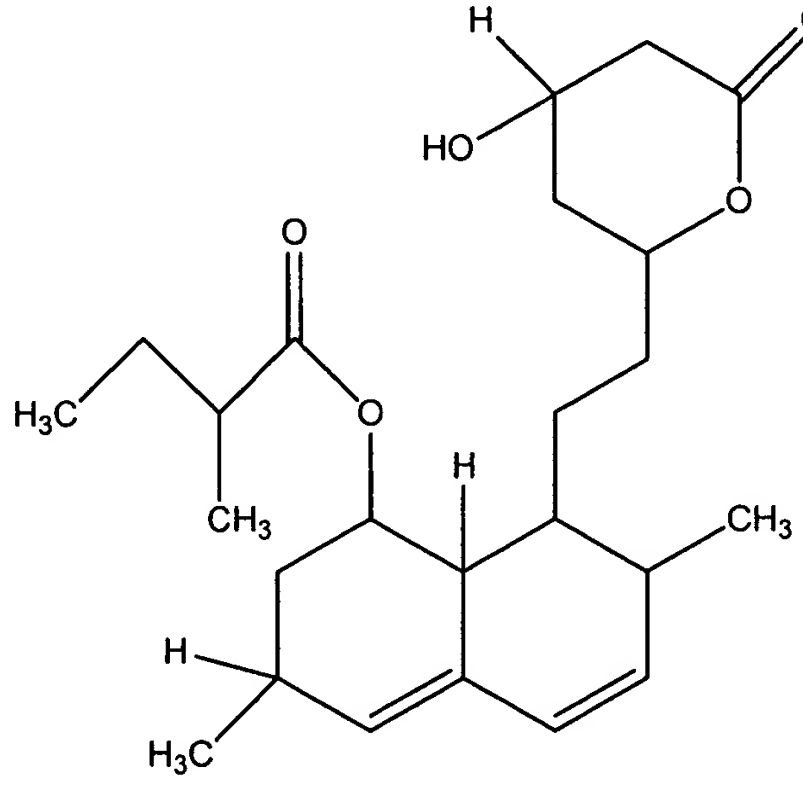
(iii) There is no teaching of structural similarity in the reference

If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, e.g., *In re Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. It is noted that the preferred active agents exemplified in Chen et al. is nifedipine in Examples 1 and 2.

It is respectively submitted that nifedipine is not similar in structure to lovastatin, fluvastatin, simvastatin, and pravastatin (the alkyl esters of hydroxy substituted naphthalenes described in Chen) and does not provide similar pharmacological activity. Nifedipine is a calcium channel blocker which is used primarily for the treatment of hypertension, while lovastatin, fluvastatin, simvastatin, and pravastatin are HMG COA reductase inhibitors for the treatment of hypercholesterolemia. Structurally, nifedipine is a dihydropyridine compound and lovastatin, fluvastatin, simvastatin, and pravastatin are lactone based structures. In order to exemplify, the structures of these lovastatin and nifedipine are set forth below in order to show the dissimilar structures of these agents:



Nifedipine



Lovastatin

Accordingly, as Chen et al. does not teach any preferred species which have structural similarity to lovastatin, fluvastatin, simvastatin, and pravastatin, there is no motivation therein to one skilled in the art to select these agents from the large genus disclosed therein.

Although the Examiner states that she has not argued that nifedipine and lovastatin have similar structures, but that the controlled release dosage form taught by Chen et al is structurally similar to Appellants, the differences in structure, pharmacological properties, and characteristics, of the species of active agent would be considered by one or ordinary skill in the art in the preparation of a controlled release formulation. Any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. See, e.g., *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of Chen et al. directed to a compound (i.e. nifedipine) that is not structurally similar to lovastatin, fluvastatin, simvastatin, and pravastatin (as discussed above) is further evidence that one skilled in the art would not be motivated to select these compounds from the genus described therein.

The broad ranges described in the present specification at Table 1 provide guidance to one of ordinary skill in the art to prepare a dosage form of the present invention with routine experimentation. One skilled in the art would appreciate that formulations of alkyl esters of hydroxy substituted naphthalenes could be prepared that do not meet the limitations of claim 1, but would generically fall with the ranges of Table 1 of the present application.

It is respectfully submitted that Chen et al. fail in the very least to teach, hint or suggest the T_{max} range recited in the present claims as no information is provided in the reference concerning a desired time to maximum plasma concentration (T_{max}) for any drug, let alone an alkyl ester of hydroxy substituted naphthalene. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that a particular T_{max} would be desirable for controlled release formulations containing an alkyl ester of hydroxy substituted naphthalene.

It is respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides

a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner is using impermissible hindsight reasoning in making this rejection.

Therefore, as Chen et al. fails to teach or suggest the presently claimed invention, the Examiner is respectfully requested to withdraw this rejection.

E. Obviousness-Type Double Patent Rejections based upon U.S. Patent No. 6,485,748.

In the Final Office Action, claims 1-13, 18-19, 21-22, 25-47, 76-77, and 80 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,485,748. In the Final Office Action, the Examiner stated that "[a]lthough US patent '748 recites a generic slightly water-soluble drug, the specification and defines lovastatin as a drug that falls within this category.

In the Advisory Action, the Examiner stated that ". . . the examiner notes that US patent does not claim the instant Tmax, however, the examiner notes that US patent's claimed dosage form is capable of providing the instantly claimed Tmax."

This rejection is traversed. Applicants note that when considering when the invention defined in the claim of an application is an obvious variation of the invention defined in the claims of a patent, the disclosure of the patent may not be used as prior art. However, the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to those portions which provide support for the claims (See MPEP 8th Edition, Revision 2, Section 804(2)(B)(1)).

It is respectfully submitted that the claims of the '748 patent fail in the very least to teach, hint or suggest the T_{max} ranges recited in the present claims. In addition, there are no dependent claims directed to alkyl esters of hydroxy substituted naphthalenes or even the general class of HMG CoA reductase inhibitors. In fact, the only dependent claims directed to specific drugs are directed to calcium channel blockers (claims 2 and 3). Furthermore, the specification of the '748 patent, like that of the Chen et al. '379 patent, only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 58 to column 3, line 16 of the '748 patent) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.). The only *in vivo* data provided in the '748 patent is data directed to dosage forms of nifidepine, which is not in any way related to, e.g., an alkyl ester of hydroxy substituted naphthalenes, as described above. None of the exemplified formulations includes a drug that is an alkyl ester of hydroxy substituted naphthalenes, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone an alkyl ester of hydroxy substituted naphthalenes. Moreover, there is no statement in either the specification or the claims of the '748 patent relating to T_{max}, or suggestion that the *in vivo* plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxy substituted napthalenes.

It is respectfully submitted that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner is using impermissible hindsight reasoning in making this rejection.

Therefore, it is respectfully submitted that the claims of the '748 patent do not teach or suggest the presently claimed invention and the Examiner is respectfully requested to withdraw the obviousness rejection over the '748 patent.

F. Obviousness Type Double Patenting Rejection Over Copending Application No. 09/435,576

With respect to the double-patenting rejection of the claims over copending Application No. 09/435,576, Applicants again note that the filing of a terminal disclaimer with respect to this patent and application will be considered upon notice that the claims are otherwise allowable.

G. Conclusion

It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance. According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephone interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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EXHIBIT A

Pharmaceutical Research, Vol. 8, No. 7, 1991

Report

Enhancement of 3-Hydroxy-3-methylglutaryl–Coenzyme A (HMG–CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form

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An extended-release osmotic dosage form was designed for gastrointestinal delivery of the water-soluble tromethamine salt of the β-hydroxyacid form of simvastatin, a potent HMG–CoA reductase inhibitor and cholesterol lowering agent. The cholesterol lowering efficacy and systemic plasma drug levels resulting from peroral administration of this dosage form, relative to a powder-filled capsule oral bolus, were evaluated in dogs. A twofold improvement in cholesterol lowering efficacy was realized with the controlled-release dosage form that was accompanied by a drug AUC and C_{max} that were 67 and 16%, respectively, of those achieved with the bolus ıge form. These results suggest that extended-release dosage ns have the potential for a dose-sparing advantage in the administration of HMG–CoA reductase inhibitors for the treatment of hypercholesterolemia.

KEY WORDS: 3-hydroxy-3-methylglutaryl–CoA reductase (HMG–CoA reductase) inhibitor; simvastatin; extended release; osmotic pump; cholesterol lowering efficacy.

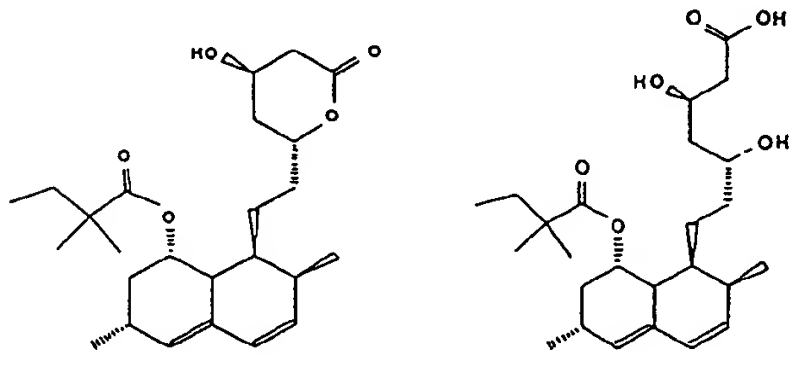
INTRODUCTION

Simvastatin (I) is a lactone that hydrolyzes to the corresponding β-hydroxyacid (II), a potent inhibitor of 3-hydroxy-3-methylglutaryl–Coenzyme A reductase (HMG–CoA reductase) and thus of de novo cholesterol synthesis (1,2) (Scheme I). As the primary site of cholesterol synthesis and regulation, the liver is the target organ for HMG–CoA reductase inhibitors. Vickers *et al.* (3) have shown that the liver extracts the lactone form of simvastatin to a much greater extent than the β-hydroxyacid form. An ideal dosing scheme would provide therapeutic levels of inhibitor to the liver at a rate that results in a hepatic extraction ratio approaching unity, thereby minimizing the systemic HMG–CoA reductase inhibitor levels. In principle, this may be accomplished by a portal drug infusion. Osmotically actuated dosage forms have been extensively investigated (4–6) as peroral drug delivery systems with similar *in vitro/in vivo* performance. Recent advances in osmotic pump technology have extended the utility of these dosage forms (7–9). In the studies reported here osmotic pump devices were designed and fabricated with microporous coats and the *in vitro* release of the water-soluble tromethamine salt of the β-hydroxyacid (i.e., tromethammonium · II) was characterized. A peroral dosing trial in dogs designed to evaluate cholesterol lowering efficacy and systemic plasma drug levels following osmotic pump dosing relative to bolus dosing of the water-soluble ammonium salt of the β-hydroxyacid (i.e., ammonium · II) was completed.

MATERIALS AND METHODS

Simvastatin (I), ammonium · II (Merck, Sharp & Dohme Research Laboratories, West Point, PA), tromethamine free base, mannitol (Aldrich Chemical Company, Milwaukee, WI), polyvinylpyrrolidone (Povidone 29-32K, GAF Corporation, Wayne, NJ), butylated hydroxyanisole (BHA; Eastman Chemical Products Incorporated, Kingsport, TN), and magnesium stearate (Fisher Scientific, Fair Lawn, NJ) were used as received. Cation-exchange resin (Dowex 50 × 8-100, 8% cross-linked styrene–divinylbenzene copolymer, Aldrich Chemical Company, Milwaukee, WI) was sequentially rinsed in a sintered glass funnel with deionized water (3 × 80 ml, 60°C), methanol (3 × 80 ml), deionized water (1000 ml), sodium hydroxide (3 *N*, 3 × 80 ml), deionized water (1000 ml), hydrochloric acid (3 *N*, 5 × 80 ml), and deionized water until the pH of the rinse water eluting out of the funnel equaled the pH of the rinse water added into the funnel. The resin was dried before use. Cellulose acetate 398-30 (CA-398-30) and cellulose acetate 320S (CA-320S) (Eastman Chemical Products, Kingsport, TN), sorbitol (Aldrich Chemical Company, Milwaukee, WI), and polyethylene glycol 400 (PEG 400, Sigma Chemical Company, St. Louis, MO) were used as received to form the coats of controlled porosity. All other reagents were reagent grade and used without further purification.

Tromethammonium · II was obtained by hydrolysis of I. Compound I (25 g, 0.06 mol) was dissolved in methanol



Compound I Compound II

Scheme I

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(150 ml). A solution of sodium hydroxide (3 g, 0.075 mol) in 20 ml water was then added to hydrolyze the lactone ring. After 5 min the solution (light orange color) was neutralized by the slow addition of phosphoric acid to a final pH of 5. The resultant II was extracted into ethyl acetate (2 × 300 ml) and dried over sodium sulfate, and the bulk solvent was evaporated. The residual oil was dried *in vacuo* (16 hr) to remove the remaining solvent. The resulting solid was accurately weighed, then dissolved in methanol (100 ml), and 1 equivalent of tromethamine free base added. Upon complete dissolution of the tromethamine, methanol was removed under vacuum (rotary evaporator, 60°C), and the oil obtained dissolved in acetone (100 ml). Crystallization was observed upon storage (25°C, 16 hr). Three crops of crystals were successively isolated (suction filtration) and dried (25°C, *in vacuo*, 18 hr) to give a 76% yield of tromethammonium · II. The X-ray powder diffraction pattern verified the isolate was crystalline. Elemental analysis was consistent with the tromethammonium · II monohydrate. FTIR and NMR spectra were consistent with the structure.

Core tablets were prepared from an aqueous granulation of tromethammonium · II, tromethamine free base, mannitol, Dowex 50 × 8-100, Povidone 29-32K, and BHA. The granulation was dried (40°C, 24 hr) and sized (No. 18 U.S. Standard Sieve). The granulation was lubed with magnesium stearate and compressed into core tablets with a ⅜-in. round standard concave die. A controlled porosity wall was applied to these core tablets by fluidized-bed (Uni-Glatt, Glatt Air Techniques, Ramsey, NJ) spray-coating techniques. The coating solution was CA-398-30, CA-320S, sorbitol, and PEG 400 dissolved in a water:methanol:methylene chloride (1:10:15, by parts) solvent blend. The core and coat compositions are summarized in Table I. The *in vitro* release (USP paddle dissolution Method 2, 50 rpm, 37°C, VanKel Industries, Edison, NJ) of tromethammonium · II from these devices was followed by two procedures. In the first procedure (Procedure A) devices were added to isoosmotic HCl buffer (900 ml, pH 1.2) for 4 hr, then transferred into isoosmotic phosphate buffer (900 ml, pH 8.0, 0.07 *M* phosphate) for the remainder of the release experiment. In the second procedure (Procedure B) devices were added to the isoosmotic phosphate buffer for the entire release experiment. At each sampling time the devices were transferred into fresh buffer (900 ml) and sodium dodecyl sulfate (SDS; 0.6%, w/w) was dissolved in the previous medium to assure solubilization of the released drug. Samples taken with and without the added SDS were compared. In all cases mass balance recovery of drug was obtained with SDS. An ~90% recovery was observed in samples that did not contain SDS.

Table I. Osmotic Pump/Tromethammonium · II Formulation Composition

Granulation component	mg/core tablet	Coat component[a]	Parts
Tromethammonium · II	25.4[b]	CA-398-30	1.00
		CA-320S	0.33
Mannitol	100	Sorbitol	0.96
Tromethamine free base	105	PEG 400	0.27
Dowex 50 × 8	45		
Povidone 29-32K	25		
Mg stearate	1.5		
BHA	0.06		

[a] 350-μm coat applied.
[b] Equivalent to 20 mg ammonium · II.

Compounds I and II were assayed by HPLC (Shimadzu Corporation, Kyoto, Japan). An acidified (0.75 ml of 70% phosphoric acid/liter of mobile phase) methanol:water (3:1, by volume) mobile phase was pumped at a rate of 1.5 ml/min through a C_8 column (25 cm, RP-8 Spheri-5, Brownlee Labs Inc., Santa Clara, CA). Peaks were detected and quantitated by UV absorbance at 238 nm. A linear detector response ($r^2 > 0.99$) with zero intercept was observed over the concentration range of interest (1–40 mg/L).

In vivo studies were performed in a crossover study in beagle dogs to determine the extent of serum cholesterol reduction associated with oral administration of tromethammonium · II released from an osmotic pump compared to an oral bolus (dry-filled capsules) of ammonium · II. Seven beagle dogs (three females and four males) were maintained on a fixed and recorded diet. In all cases the dogs were fed prior to blood sampling and dosage form administration. The diet was initiated 1 week prior to baseline blood sampling. Blood was sampled on the second and fifth days of each week throughout the trial. Blood samples were collected for 3 weeks prior to the initiation of dosing to establish untreated baseline cholesterol levels. Oral bolus dosing (100 mg/day of ammonium · II for 28 days) was initiated first to confirm that the specific animals selected were responsive to the drug before administering the drug in the controlled-release osmotic pump dosage form. Upon termination of dosing blood sampling was continued to confirm return to baseline cholesterol levels as plasma levels of the HMG–CoA reductase inhibitor returned to zero. Once return to baseline levels was demonstrated, oral dosing of tromethammonium · II in the osmotic pump configuration was initiated. Each dog received five devices per day as a single dose for 28 days, to realize a total dose of tromethammonium · II equivalent to 100 mg ammonium · II per day. All serum cholesterol assays were performed by a contract laboratory (Lawrence Memorial Hospital, Lawrence, KS) utilizing a cholesterol esterase procedure standardized against the Abell–Kendal reference method (10). On day 16 (steady state) of both dosing regimes blood samples were taken at 0.5, 1, 2, 3, 4, 6, and 24 hr and analyzed by an enzyme inhibition assay (1,11) for the total amount of HMG–CoA reductase inhibitors (including metabolites) present in plasma. From this data C_{max} and AUC pharmacokinetic parameters were calculated.

RESULTS AND DISCUSSION

Compound I has a water solubility of 0.03 mg/ml in water at room temperature. This low solubility would preclude effective delivery from an osmotic pump dosage form. However, tromethammonium · II has a water solubility of >40 mg/ml in water at room temperature and becomes a feasible candidate for osmotic pump delivery. The *in vitro* release profiles of tromethammonium · II from the osmotic pump formulation (Table I) are shown in Fig. 1. Release profiles

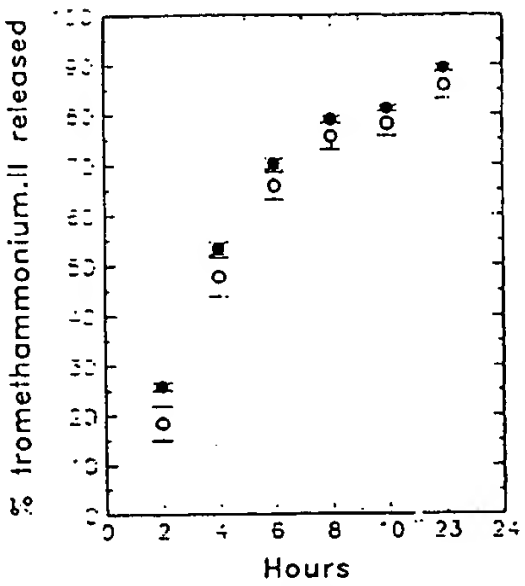

Fig. 1. *In vitro* release profiles from tromethammonium · II/osmotic pump devices as determined by Procedure A (○; $n = 6$) and Procedure B (●; $n = 6$). Standard deviations are included.

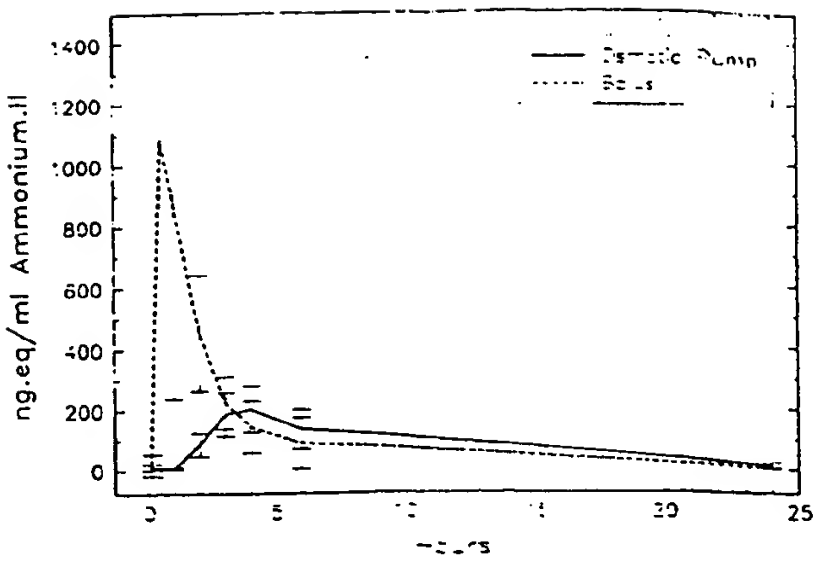

Fig. 2. Mean plasma concentration time profiles (± SD; $n = 7$) following administration of bolus or osmotic pump dosage forms.

generated by Procedure A, designed to simulate the extremes of the variable pH conditions within the gastrointestinal tract, and Procedure B (constant pH conditions) were very similar. Any conversion of the water-soluble tromethammonium · II into the water-insoluble, and hence poorly releasable, lactone at low pH was insufficient to alter substantially the observed release profiles. The devices released ~60% of the drug load *in vitro* with zero-order kinetics over a 6-hr period. Within 10 hr, 75–80% of the drug was released, with the remaining drug released at a substantially slower rate. After 24 hr, ~90% of the drug load had been released.

The *in vivo* cholesterol lowering efficacy results of the osmotic pump compared to the bolus dosage form have been summarized in Table II. The osmotic pump dosing regime was twice as effective (statistically significant; one-way ANOVA with post hoc Tukey *W* comparison; $P < 0.05$) at lowering cholesterol levels as the bolus dosing regime at an equivalent total daily dose. The mean total plasma HMG–CoA reductase inhibitor concentration time profiles (blood samples collected on day 16 of the respective dosing regimes) are shown in Fig. 2 and the relevant pharmacokinetic parameters are given in Table III. Area under the HMG–CoA reductase inhibitor · time curve (AUC) values were calculated using the trapezoidal rule to the last measurable inhibitor concentration. The observed mean AUC after the osmotic pump dosing was 67% that of the bolus (one-way ANOVA with post hoc Tukey *W* comparison; $P < 0.10$). The mean C_{max} after the osmotic pump dosing was 16% that of the bolus (one-way ANOVA with post hoc Tukey *W* comparison; $P < 0.05$). In the present studies, C_{max} and AUC represent measures of systemic drug burden that have been substantially reduced through administration of the controlled release osmotic pump dosage form. Combining the twofold improvement in efficacy with the lowered systemic drug burden leads to a 3- to 12-fold therapeutic advantage from the controlled-release dosage form. The increased therapeutic efficacy from the extended release osmotic pump relative to the bolus at the same daily dose suggests that a dose-sparing advantage may be possible through the controlled release of HMG–CoA reductase inhibitors.

Table II. Maximum Reduction of Serum Cholesterol in Dogs Following 28 Days' Administration of Ammonium · II[a]/Boluses or Tromethammonium · II[b]/Osmotic Pumps

Dog No.	Baseline cholesterol (mg/100 ml)	Maximum percentage decrease in serum cholesterol	
		Bolus	Osmotic pumps
02	186	9	36
03	200	21	31
37	218	24	44
66	203	10	25
81	160	23	43
84	185	18	23
85	192	18	37
Mean ± SD	192 ± 18	17 ± 6	34 ± 8

[a] Dose, 100 mg/day.

Table III. Pharmacokinetic Summary[a]

Dog No.	C_{max} (ng · eq/ml)		AUC (ng · eq · hr/ml)	
	Bolus	Osmotic pump	Bolus	Osmotic pump
01	571	203	3520	2450
03	1950	213	4060	2430
37	249	274	3340	3180
66	566	127	3910	990
81	652	113	4690	1140
84	990	187	5100	1130
85	3940	318	4450	2930
Mean[b]	1270	205	3010	2035
SD	1300	74	1105	926

[a] Sixteenth dosing day.
[b] Geometric mean.

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